17. (amended once) A method for the treatment of a disease or disorder in a mammal in which the extravasation of leukocytes plays a role, comprising administering to a mammal suffering from such a disease or disorder a therapeutically effective amount of a compound according to Claim 16.

18 (amended once). A method according to Claim 17 wherein said disease or disorder is selected from the group consisting of inflammatory arthritis, allograft rejection, diabetes, inflammatory dermatoses, asthma and inflammatory bowel disease.

REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is requested respectfully.

Applicants note that the Summary Sheet accompanying the present Office Action indicated that the Action is Final, although the comments indicated that the Action is non-final because new art was applied. Following a telephonic discussion with the undersigned attorney, an Interview Summary Record was issued on July 16, 2001, which states that the action is non-final, and that the shortened statutory period is two months from the July 16, 2001 mailing date of the Interview Summary Record.

Claims 2 to 22 are pending. Claims 16, 17, and 18 have been amended. No claims have been canceled or added. Applicants acknowledge with appreciation the withdrawal of the rejections under 35 U.S.C. §§101 and 102, as well as certain rejections under §112, second paragraph. The present Office Action includes rejections under 35 U.S.C. §§§101, 102, and 112, first and second paragraph, which are discussed in detail below.

Discussion of the Rejections Under Section 102

Claims 2 to 8 and 16 to 22 have been rejected as being anticipated in view of Astles, International Publication No. WO 99/23063 ("the 063 application"). Applicants note, however, that although the 063 application has a purported priority date of October 31, 1997, the application did not publish until May 14, 1999, over 5 months after Applicant's earliest priority date. As such, the comment in the Office Action that if the 063 application issued as a U.S. patent, it would somehow be a 102(b) reference, is misplaced. Indeed, under no circumstances could the 063 application qualify as 102(b) prior art because it was not "patented or described in a printed publication...more than one year prior" to the priority date of Applicants' application. To the contrary, under the present circumstances, the 063 application is not even available as prior art under 102(a). Thus, Applicants respectfully request withdrawal of the rejection in view of the 063 application.

Claims 3, 4, 7 to 10, and 16 have been rejected as being anticipated in view of Kato, et al. *Tetrahedron Letters*, 29(49), 6465-6 (1988). Claims 2 to 8 and 16 to 22 have been

rejected as being anticipated in view of Scott et al., U.S. Patent No. 6,096,773. Claims 2 to 8 and 16 to 22 have been rejected as being anticipated in view of Alig et al., U.S. Patent No. 5,399,585. It is basically asserted in the Office Action that the compounds taught in the aforementioned publications are encompassed in the Applicants' aforementioned claims.

In order to advance prosecution, claim 16 has been amended in a manner that Applicants believe renders these rejections moot. Particularly, claim 16 has been amended to recite that R^3 is selected from an optionally substituted C_{3-10} cycloaliphatic group; an optionally substituted C_{7-10} polycycloaliphatic group; an optionally substituted C_{3-10} heterocycloaliphatic group; an optionally substituted C_{7-10} heteropolycycloaliphatic group; an optionally substituted aromatic group; and an optionally substituted C_{1-9} heteroaromatic group. Support for this amendment is provided, for example, on page 20, lines 17 to 25 of the specification. It will be recognized that the cited art does not teach or suggest such compounds as the art is universally directed to compounds wherein, by analogy to the compounds embodied in claim 16, R^3 is an aliphatic group.

Applicants also note that this amendment renders moot the art rejections in view of Suvorov, et al., *Zhur. Obsh. Khim.*, 30, 2051-5 (1960) and Wasserman, et al., *J. Am. Chem. Soc.*, 105(6), 1697-8 (1983), cited in the Office Action mailed July 16, 2001. As such, provisos (2) and (3) have been deleted from claim 16. With respect to proviso (1) in claim 16, Applicants have amended the definition of L^1 in claim 16 to recite that variable L^1 is a covalent bond or a linker atom or group selected from $-CON(R^2)-$, $-S(O)_2N(R^2)$, $-N(R^2)-$, and -O-. Because this

amendment renders moot the rejections in view of Rodionov, et al., *Zhur. Obsh. Khim.*, 27, 2234-8 (1957) and Mamaev, *Zhur. Obsh. Khim.*, 27, 1290-3 (1957), proviso (1) has also been deleted from claim 16. Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under Section 102.

Discussion of the Rejections Under Section 112, first paragraph

Claims 2 to 22 have been rejected for containing subject matter not described in such a way as to reasonably convey that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action alleges that the provisos added to claim 16 by the Amendment filed April 25, 2001, lack support in the description. Although Applicants disagree that the provisos are not supported by the specification, the provisos have been deleted in favor of the new amendments to claim 16. *See*, discussion of rejections under §102, *supra*. As such, Applicants believe the rejection for lack of written description is moot.

Claims 17 to 20 have been rejected for containing subject matter not described in such a way as to enable one skilled in the art to make and use the claimed compounds. Although the Office Action concedes that these claims are enabled for the treatment of diseases in which extravasation plays a role, it is maintained that the claims are not enabled for prevention of the same. In the Reply filed April 25, 2001, Applicants submitted that the present Office Action provides no such technical reasoning to support this conclusion. Applicants teach that control of

the physical interaction of inflammatory leukocytes plays an important role in the regulation of immune and inflammatory responses and that these interactions are mediated by specific cell surface molecules including integrins. *See*, for example, page 1, lines 6 to 11 of the specification. Applicants also teach that in one particular subgroup of integrins, the α4 integrins, there is clear evidence that α4β1 (VLA-4) binds to an adhesion molecule known as VCAM-1, which is frequently up-regulated at sites of inflammation. *See*, for example, page 2, lines 17 to 20 of the specification. Thus, it would be expected by one of ordinary skill in the art that if a VLA-4 inhibitor is given prior to a disease developing, the necessary integrin mediated interactions that lead to the disease are prevented, hence providing a method of prophylaxis. Nevertheless, notwithstanding the impropriety of the rejection, Applicants have amended claim 17 to delete the term "prophylaxis" solely for purposes of facilitating prosecution.

Claims 17 and 18 have also been rejected because, according to the Office Action, Applicants have not enabled the treatment of multiple sclerosis (MS). In the Reply filed April 25, 2001, Applicants pointed out that in an MS animal model (experimental autoimmune encephalomyelitis (EAE)) antibodies against VLA-4 are effective in prevention of EAE. *See*, Yednock, *Nature*, 356, 63 (1992). Nevertheless, the Office Action calls into question the degree to which Applicants compounds will be efficacious. It is well-established, however, that pharmaceutical inventions usually require further research and development. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Were such inventions not patentable long before being optimized or ready for human use, the incentive to fully research and develop vital drugs and potential cures

would be completely removed. *Id.* at 1567-68. Applicants have provided, for example, on page 54, line 23 to page 56, line 27 of the specification, assays that may be used to determine biological activity and specificity together with the levels for activity that are preferably obtained for the compounds to be suitable for the claimed use. Because the Office Action provides no credible reason for doubting that compounds possessing activity would be useful in treating MS to some measurable extent, Applicants respectfully submit that the treatment of MS is, in fact, enabled. Nevertheless, in an effort to advance prosecution, multiple sclerosis has been deleted from claim 18. Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under Section 112, first paragraph.

Rejections Under Section 112, second paragraph

The Office Action includes various objections to the form of Applicants' claims accompanied by a statement that the claims are indefinite. It is submitted respectfully that one of ordinary skill in the art would have no difficulty understanding the metes and bounds of Applicants' original claims, and the terminology used therein, as they are both clear and definite.

The term "solvates" has been repeatedly objected to as reading on an unlimited and undefined number of solvent complexes. Again, Applicants respectfully submit that the Office Action confuses breadth with indefiniteness. In this connection, the Office Action discusses many aspects in which various solvates may differ including how tightly bound the solvent is, how many molecules exist in the lattice, etc. The Office Action, however, does not so

much as question that one of ordinary skill in the art would have any difficulty appreciating the meaning and scope of the term itself. To the contrary, the discussion in the Office Action establishes that the term is well-understood in the art. Thus, although numerous forms of solvates are possible, the language employed defines the patentable subject matter in a manner that one of ordinary skill in the art would appreciate, which is all that is required to satisfy 35 U.S.C. §112, second paragraph.

The Office Action asserts that the term "optionally substituted" is not understood inasmuch as it is unclear what substituents are encompassed by the claims. In the Reply filed April 25, 2001, Applicants respectfully submitted that claims must be read in view of the specification. Indeed, the definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure and the claim interpretation that would be given by one possessing the ordinary level of skill in the art. *In re Marosi*, 710 F.2d 799 (Fed. Cir. 1983). Nevertheless, the Office Action appears to insist upon reading the claims in a vacuum. This is evidenced by the inclusion in the Office Action of a dictionary passage defining a "substituent" as an "atom or radical." Although Applicants do not disagree that a substituent may be an atom or a radical, Applicants do not agree that a dictionary is the totality of guidance available to the skilled artisan for interpreting the claims. To the contrary, optional substituents for Ar^1 are provided, for example, on page 7, line 5 to page 9, line 36 of the specification and optional substituents for aliphatic and heteroaliphatic groups are provided, for example, on page 10, line 27 to page 11, line 3 of the specification.

Although the Office Action does not appear to dispute the presence of these definitions, it is asserted that these groups must be inserted in the claims because, among other reasons, Applicants specifically define other groups in the claims, such as R^b. Group R^b, however, is not an "optional substituent"--it is part of the group $-(Alk^b)_mR^b$. With respect to the additional reasons enumerated in the Office Action, Applicants are unclear as to how the definitions of the intended substituents are "conflicting" and "open." To the extent the rejection is maintained, Applicants respectfully request clarification in this regard.

The Office Action objects to other terms used in the claims, including "heteroaliphatic", "cycloaliphatic", "heterocycloaliphatic", "polycycloaliphatic", and "heteropolycycloaliphatic" as "improper" and "oxymorons." In support of this position, the Office Action asserts that the only term that could be appreciated by one of ordinary skill in the art is the word "aliphatic," because it is found in the dictionary. Applicants respectfully submit, however, that simply because a word is not found in the dictionary, does not render it *per se* "improper" or an "oxymoron." To the contrary, Applicants are at a loss to understand how the Office Action can reasonably suggest that one of ordinary skill in the art would fail to appreciate the intended meaning of, for example, the term "heteroaliphatic" or "cycloaliphatic", particularly when these terms (as well as the other terms) ***are defined in the specification***.

On this point, the Office Action asserts that "[a]n aliphatic group may not contain rings or heteroatoms." As a threshold matter, Applicants do not define the term "aliphatic" as containing heteroatoms or rings. Rather, the terms "heteroaliphatic" and "cycloaliphatic" contain

heteroatoms and rings, respectively. Thus, technically speaking, Applicants do not use the specific term "aliphatic" in a manner that is contrary to the definition provided in the Office Action.

What the Office Action actually appears to take issue with is the use of the prefixes such as hetero and cyclo, and the like, as modifying a root (aliphatic) which purportedly has an art-recognized meaning. Applicants fail to see how the modification of a word through the use of a prefix would prevent the skilled artisan from recognizing the meaning of the word. Indeed, even assuming, *arguendo*, that Applicants did use a term in a manner contradictory to the art-recognized meaning, it would not be "improper" under the patent laws. The Federal Circuit has made clear that "consistent with the well-established axiom in patent law that a patentee is free to be his or her own lexicographer, a patentee may use terms in a manner *contrary to* or *inconsistent with* one or more of their ordinary meanings. *Hormone Research Foundation, Inc., v. Genentech, Inc.*, 904 F.2d 1558 (Fed. Cir. 1990) (emphasis added); *see also*, M.P.E.P. §2173.05(a). Thus, Applicants respectfully submit that the rejection of these terms is misplaced and should be withdrawn.

The Office Action also objects to the phrase "an ester or amide" of a carboxylic acid as indefinite. Although Applicants believe one of ordinary skill in the art would appreciate the meanings of these terms, Applicants have amended the claims to recite "carboxylic ester or carboxylic amide" to address the Examiner's concerns. One of ordinary skill in the art would appreciate the meanings of these terms in view of the definitions of esters of formula CO_2Alk^1 on

page 14, line 24 to page 15, line 2, and the definitions of amides of formula $CONR^5R^6$ provided, for example, on page 7, line 34 to page 8, line 4 of the specification. Support for this amendment is provided, for example, on page 6, lines 1 to 2.

Claim 17 stands rejected because, according to the Office Action, the phrase "a disease or disorder in a mammal in which the extravascation [sic, extravasation] of leukocytes plays a role" is indefinite. In the Reply filed April 25, 2001, Applicants pointed out that on page 22, lines 8 to 11 of the specification, Applicants exemplify which diseases involve inappropriate leukocyte extravasation. Particularly, such diseases include inflammatory arthritis, including rheumatoid arthritis, vasculitis, or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma, and inflammatory bowel disease. In view of this statement, Applicants request clarification as to how, once armed with this definition, the skilled artisan would fail to appreciate in which diseases leukocytes play a role.

The Office Action also states that because the claims do not set forth steps for determining in which diseases extravasation of leukocytes plays a role, undue experimentation would be necessary to determine the same. Although this aspect of the rejection is couched in terms of 112, second paragraph, the Office Action appears to question the degree to which one skilled in the art would be able to practice the claim. This is evidenced by the passages in the Office Action criticizing Applicants specification for not teaching conditions for "successful treatment", "dosage regimens", and demonstrating *in vitro* vs. *in vivo* activity. Such questions,

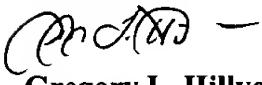
however, are not relevant to whether or not the skilled artisan would understand the metes and bounds of the claims. Thus, it is respectfully submitted that the Office Action confuses the definiteness requirement of §112, second paragraph with the enablement requirement of §112, first paragraph. Again, the definiteness of claim language must be analyzed in light of the content of the specification and the claim interpretation that would be given by one possessing the ordinary level of skill in the art. *In re Marosi*, 710 F.2d 799 (Fed. Cir. 1983). As noted above, the specific disease states are identified in the specification, and as such, the claim is not indefinite. In view of the above amendments and remarks, reconsideration and withdrawal of the rejection under Section 112, second paragraph, is requested respectfully.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections and an allowance of the pending claims is requested respectfully.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 16, 17, and 18 have been amended as follows.

16. (amended twice) A compound of formula (1):

$$Ar^1(Alk^a)_rL^1Ar^2CH(R^1)C(R^a)(R^{a'})R \qquad (1)$$

wherein

Ar^1 is an optionally substituted aromatic or C_{1-9} heteroaromatic group containing one to four heteroatoms seleted from oxygen, nitrogen, and sulfur;

L^1 is a covalent bond or a linker atom or group selected from -CON(R^2)-, -S(O)$_2$N(R^2), [-C(O)O-,] -N(R^2)-, and -O-;

R^2 is a hydrogen atom or a C_{1-3} alkyl group;

Ar^2 is an optionally substituted phenylene group;

R^1 is a group selected from -NHCOR^3, -NHSO$_2R^3$, -NHR^3, -NHC(O)OR^3, -NHCSR^3, -NHCON(R^3)(R^{3a}), -NHSO$_2$N(R^3)(R^{3a}), and -NHCSN(R^3)(R^{3a});

R^3 is [an optionally substituted C_{1-6} aliphatic group, an optionally substituted C_{1-6} heteroaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, -S(O)$_2$-, -N(R^8)- (where R^8 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group), -C(O)NR^8-, -OC(O)N(R^8)-, -CSN(R^8)-, -N(R^8)CO-, -N(R^8)C(O)O-, -N(R^8)CS-, -S(O)$_2$N(R^8)-, -N(R^8)S(O)$_2$-, -N(R^8)CON(R^8)-, -N(R^8)CSN(R^8)- and -N(R^8)SO$_2$N(R^8)-;] an optionally substituted C_{3-10}

cycloaliphatic group, an optionally substituted C_{7-10} polycycloaliphatic group, an optionally substituted C_{3-10} heterocycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$; an optionally substituted C_{7-10} heteropolycycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$; an optionally substituted aromatic group, or an optionally substituted C_{1-9} heteroaromatic group containing one, two, three or four heteroatoms seleted from oxygen, nitrogen, and sulfur;

R^{3a} is a hydrogen atom, an optionally substituted C_{1-6} aliphatic group, an optionally substituted C_{1-6} heteroaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$; an optionally substituted C_{3-10} cycloaliphatic group, an optionally substituted C_{7-10} polycycloaliphatic group, an optionally substituted C_{3-10} heterocycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-,

-C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$; an optionally substituted C_{7-10} heteropolycycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$; an optionally substituted aromatic group, or an optionally substituted C_{1-9} heteroaromatic group containing one, two, three or four heteroatoms seleted from oxygen, nitrogen, and sulfur;

R^a and $R^{a'}$, which may be the same or different, are each independently selected from a hydrogen or halogen atom or an optionally substituted straight or branched alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, alkylthio or $-(Alk^b)_mR^b$ group (in which Alk^b is a C_{1-3} alkylene chain, m is zero or the integer 1, and R^b is -OH, -SH, $-NO_2$, -CN, $-CO_2H$, $-CO_2R^c$ (where R^c is an optionally substituted straight or branched C_{1-6} alkyl group), $-SO_3H$, $-SOR^c$, $-SO_2R^c$, $-SO_3R^c$, $-OCO_2R^c$, -C(O)H, $-C(O)R^c$, $-OC(O)R^c$, $-C(S)R^c$, $-NR^dR^e$ (where R^d and R^e, which may be the same or different, are each a hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl group), $-CON(R^d)(R^e)$, $-OC(O)N(R^d)(R^e)$, $-N(R^d)C(O)R^e$, $-CSN(R^d)(R^e)$, $-N(R^d)C(S)R^e$, $-S(O)_2N(R^d)(R^e)$, $-N(R^d)SO_2R^e$, $-N(R^d)CON(R^e)(R^f)$ (where R^f is a hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl group), $-N(R^d)C(S)N(R^e)(R^f)$ or $-N(R^d)SO_2N(R^e)(R^f)$ group);

Alk^a is an optionally substituted C_{1-6} aliphatic or C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, and $-N(R^8)SO_2N(R^8)-$;

r is zero or the integer 1;

R is a carboxylic acid (CO_2H), [or an ester group or amide group] a carboxylic ester group, or carboxylic amide group;

and the salts, solvates, hydrates and N-oxides thereof.[;

with the provisos that:

(1) when Ar^1 is unsubstituted phenyl, r is zero, L^1 is C(O)O, Ar^2 is unsubstituted 1, 4-phenylene or 1,4-phenylene substituted with 3-fluoro, R^a and $R^{a'}$ are hydrogen, R is CO_2H, and R^1 is $NHCOR^3$, then R^3 is other than unsubstituted phenyl;

(2) when r is zero, L^1 is -O-, Ar^2 is 1,3-phenylene substituted with 4-methoxy, R^a and $R^{a'}$ are hydrogen, and R is CO_2CH_3, R^1 is $NHCOR^3$, R^3 is tert-butyloxy, then Ar^1 is other than phenyl substituted in the 4-position with 3-methoxy-3-oxo-1-propenyl; and

(3) when Ar^1 is phenyl substituted in the 4-position with methoxy, r is zero, L^1 is -O-, R^1 is $NHCOR^3$, R^3 is methyl, R^a and $R^{a'}$ are hydrogen, and R is CO_2Et, then Ar^2 is other than 3,5-dinitro or 3,5-diiodo substituted.]

17 (amended once). A method for the [prophylaxis or] treatment of a disease or disorder in a mammal in which the extravasation of leukocytes plays a role, comprising administering to a mammal suffering from such a disease or disorder a therapeutically effective amount of a compound according to Claim 16.

18 (amended once). A method according to Claim 17 wherein said disease or disorder is selected from the group consisting of inflammatory arthritis, [multiple sclerosis,] allograft rejection, diabetes, inflammatory dermatoses, asthma and inflammatory bowel disease.